REMARKS

Claims 1-6, 8-11 and 13-18 currently appear in this application. The Office Action of February 1, 2008, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims

Rejections under 35 U.S.C. 112

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

As claim 7 has been cancelled, this rejection is now moot.

Claims 10-12 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

This rejection is respectfully traversed. Claim 10 has been amended to recite specific diseases, and claim 11 has been amended to restrict the diseases treated to cardiac insufficiency and renal insufficiency, myocardial infarction, peripheral vascular disease, and diabetic proteinuria. It has been demonstrated that the claimed compounds have a high

affinity and selectivity for APA, while the compounds have no activity with respect to akminopeptidase (APN).

As the Examiner is well aware, MPEP Section 2164.02 specifically states, "Am *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention ...if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." It is respectfully submitted that one skilled in the art would readily correlate the high affinity and selectivity of the claimed compounds for APA with primary or secondary arterial hypertension, cardiac insufficiency and renal insufficiency, myocardial infarction, a peripheral vascular disease, diabetic proteinuria.

Claims 10-12 and 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. Claims 10 and 11 have been amended to recite the diseases treated more specifically. Claim 12 has been cancelled. Claims 15-20 relate to specific compounds used,

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that the specification only provides inhibition data for APA, and that "selectively" is used when more than one receptor is tested for inhibitory activity by specific compounds.

This rejection is respectfully traversed. The specification as filed states at page 2, lines 14-20:

> The invention shows that, unexpectedly, the introduction of a group R_2 into a nonpeptide structure results in the production of APA-inhibiting compounds that have a high affinity and selectivity for APA, whereas these compounds have no activity with respect to aminopeptidase (APN).

A rennin-angiotensin system is present in the central nervous system and controls cardiovascular functions and body fluid homeostasis. Aminoeptidase A (APA) is responsible for the transformation of angiotensin II into angiotensin III, while Aminopeptidase N (APN) is responsible for the transformation of angiotensin III into angiotensin IV

Previous studies in rats have shown that angiotensin III, generated by APA, is one of the main effector peptides of the brain rennin-angiotensin system (RAS), exerting a stimulatory control over blood pressure. Therefore, it is desirable to obtain selective inhibitors of APA.

Previous studies have also been reported that a high selective inhibitor of APA is the compound EC33 referred to on page 58 of the instant application. As EC33 does not cross the blood-brain barrier, a dimer-precursor thereof, RB150, also referred to on page 58 was designed, which dimer can be cleaved *in vivo* to release the selective inhibitor EC33.

These studies also show the importance or providing selective molecules which are able to block the rennin-angiotensin system by inhibiting the formation of angiotensin III by action of an inhibitor of APA, and not by inhibiting the degradation of angiotensin II, as performed by an APN inhibitor.

The present application claims dimer compounds which structurally differ from RB150 but the same rationale applied with regard to their affinity towards APA. As the herein claimed compounds show *in vitro* a high affinity towards APA, which is even higher than that of EC33. it is highly predictable by one skilled in the art that the claimed compounds are selective for APA.

Submitted herewith are copies of Reaux et al., *PNAS*, 1999, **23**, 13415-13420 (see in particular the abstract and introductory part on page 13415), and of Bodineau et al., *Hypertension*, March 24, 2008 (see in particular the scheme on

top of page 2 and the following discussion on page 2) to support the above rationale.

Claim Objections

Claims 6, 14, 16, 18 and 20 are objected to because the examiner alleges that too many numbers are present in the compound names.

It is respectfully submitted that the numbering of the chemical compounds is correct, as the compounds are dimers, that is, two-part compounds linked through a disulfide bond. On each side of the disulfide bond, the carbon atoms are numbered as a function of their location with respect to the sulfonic acid group. Each of these carbons ay have the same or different stereochemistry. For instance, in the claimed compounds, the number 3 and 3' relate to the carbon atoms linked to the NH_2 group, and both of them have an (S) configuration. Numbers 4 and 4' relate to the first carbon atom close to the sulfur atom, and both carbon atoms have an (S) configuration.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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